Select Agent Rule - A Satellite Broadcast

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Study Booklet

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PROGRAM DESCRIPTION

The Department of Health and Human Services has published regulations regarding access, use and transfer of select agents for research purposes. These regulations are designed to (1) Ensure that these infectious agents and toxins are shipped only to institutions or individuals equipped to handle them appropriately; (2) Transfer of these agents is to those who have legitimate reasons to use them, and, (3) A system is implemented whereby scientists and researchers involved in legitimate research may continue transferring these agents without undue burdens.

The program will include information about the registration process, how to document the transfer of select agents, verification procedures and agent disposal requirements, as well as research and clinical exemptions.

TARGET AUDIENCE

This program will be of interest to individuals responsible for laboratory research or safety in the following types of facilities: biotech firms, universities or other teaching institutions, veterinary institutions, pharmaceutical firms, or other laboratories working with or transferring any microorganisms or toxins classified as "select agents."

LEARNING OBJECTIVES

Upon completion of the program, participants will be able to:

- Summarize the rationale for regulating the movement of biological agents.
- Discuss the general requirements of the Select Agent Rule.
- Determine whether their facility must register to comply with the regulations.
- Complete an application packet.
- Describe the components of a self assessment in both BSL-2 and BSL-3 facilities and laboratories working with toxins.
- Review the registration and inspection process.
- Complete the forms and package select agents necessary for transfer.

INTRODUCTION TO THE SELECT AGENT RULE

Overview: The Department of Health and Human Services has published regulations regarding access, use and transfer of select agents for research purposes. These regulations are designed to (1) Ensure that these infectious agents and toxins are shipped only to institutions or individuals equipped to handle them appropriately; (2) Transfer of these agents is to those who have legitimate reasons to use them, and, (3) A system is implemented whereby scientists and researchers involved in legitimate research may continue transferring these agents without undue burdens.

The Regulation: Title 42 CRF Part 72.6 (Additional Requirements for Facilities Transferring or Receiving Select Agents) stems from the "Antiterrorism and Effective Death Penalty Act of 1996" which requires the Secretary of Health and Human Services to regulate the transfer of certain biological agents ("select agents") harmful to humans. The Centers for Disease Control and Prevention (CDC) is responsible for the implementation of this regulation.

The regulation includes six fundamental components:

1. A list of biological agents ("select agents") that have the potential to pose a severe threat to public health and safety.
    - Approximately 40 viruses, bacteria, rickettsia, fungi, and toxins are on the list of select agents. The transfer of these agents is controlled in the United States.

2. Registration of facilities prior to the transfer of select agents:
    - Registration requires that facilities submit information to the CDC that demonstrates that the facility is equipped and capable of safely handling the select agent. This application for registration must be sent to the CDC, Office of Health and Safety, Laboratory Registration/Select Agent Transfer (LR/SAT) Program. The LR/SAT Program is responsible for registration and on site inspections.

3. Transfer requirements:
    - Prior to transfer, both the shipper and the receiver must be registered with the LR/SAT Program or meet the requirements for exemption. Registered facilities are issued a unique registration number which must be used in the transfer process of these agents from one facility to another. Transfers of select agents are documented using a special form which includes information on both facilities, the agent being transferred, and the proposed use of the agent.

4. Verification procedures including audit, quality control, and accountability mechanisms:
    - Each facility shipping or receiving a select agent must have a "responsible facility official." This official must sign each request, certifying that the requestor of the agent is officially affiliated with the facility and that the laboratory meets guidelines for working with the requested agent. The "responsible facility official" sending the agent is required to verify that the receiving facility holds a currently valid registration number and that they are registered with the CDC for the specific agent being requested from them.

5. Agent disposal requirements:
    - Facilities must have in place procedures for the appropriate disposal of select agents. Upon termination of the use of a select agent, the agent must be transferred to another registered facility or destroyed on site. Consumed or destroyed agents must be reported to CDC.

6. Research and clinical exemptions:
    - Specific attenuated vaccine strains and toxins used for biomedical research purposes are exempt. Clinical laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 that utilize these select agents for diagnostic, reference, verification or proficiency testing purposes are exempt. The transfer of clinical specimens for diagnostic, reference, or verification purposes is also exempt.

THE LIST OF SELECT AGENTS
Appendix A to 42 CFR 72.6

Viruses

1. Crimean-Congo haemorrhagic fever virus
2. Eastern Equine Encephalitis virus
3. Ebola viruses
4. Equine Morbillivirus (Hendra virus)
5. Lassa fever virus
6. Marburg virus
7. Rift Valley fever virus
8. South American Haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
9. Tick-borne encephalitis complex viruses
10. Variola major virus (Smallpox virus)
11. Venezuelan Equine Encephalitis virus
12. Viruses causing hantavirus pulmonary syndrome
13. Yellow fever virus

Bacteria

1. *Bacillus anthracis*
2. *Brucella abortus, B. melitensis, B. suis*
3. *Burkholderia (Pseudomonas) mallei*
4. *Burkholderia (Pseudomonas) pseudomallei*
5. *Clostridium botulinum*
6. *Francisella tularensis*
7. *Yersinia pestis*

Rickettsiae

1. *Coxiella burnetii*
2. *Rickettsia prowazekii*
3. *Rickettsia rickettsii*

Fungi

1. *Coccidioides immitis*

Toxins

1. Abrin
2. Aflatoxins
3. Botulinum toxins
4. *Clostridium perfringens* epsilon toxin
5. Conotoxins
6. Diacetoxyscirpenol
7. Ricin
8. Saxitoxin
9. Shigatoxin
10. Staphylococcal enterotoxins
11. Tetrodotoxin
12. T-2 toxin

BSL RECOMMENDATIONS FOR SELECT AGENTS

Supplement to CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories*, 4th ed. (BMBL). Summary of biosafety level (BSL) recommendations for Select Agent Bacteria, Viruses, Rickettsiae and Fungi listed in Appendix A to Part 72* (vacc=vaccine required)

Select Agent	Biosafety Level Clinical Specimens	 / Propagation	 / Animal Work	Immuno-prophylaxis
Viruses				
Crimean-Congo hemorrhagic fever virus	4	4	4	
Eastern Equine Encephalitis virus	2	2-3	3 + vacc	vaccine (IND)[A]
Ebola viruses	4	4	4	
Equine Morbillivirus (Hendra virus)	3-4	4	4	
Lassa fever	4	4	4	
Marburg virus	4	4	4	
Rift Valley fever virus[B]	3 + HEPA	3 + HEPA	3 + HEPA	vaccine (IND)
South American hemorrhagic fever viruses				
Junin	3+vacc+HEPA	3+vacc+HEPA	3+vacc+HEPA	vaccine (IND)
Machupo	4	4	4	
Sabia	4	4	4	
Flexal	3	3	3	
Guanarito	4	4	4	
Tick-borne encephalitis complex viruses				
Absettarov[C]	3 + vacc	3 + vacc	3 + vacc	vaccine (IND)
Hanzalova[C]	3 + vacc	3 + vacc	3 + vacc	vaccine (IND)
Hypr[C]	3 + vacc	3 + vacc	3 + vacc	vaccine (IND)
Kumlinge[C]	3 + vacc	3 + vacc	3 + vacc	vaccine (IND)
Kyasanur Forest disease	4	4	4	
Omsk hemorrhagic fever	4	4	4	
Russian Spring-Summer encephalitis	4	4	4	
Venezuelan Equine Encephalitis virus	3 + HEPA	3 + HEPA	3 + HEPA	vaccine (IND)
Variola major virus (Smallpox virus)	4	4	4	vaccine
Viruses causing hantavirus pulmonary syndrome	3	3-4	3-4	
Yellow fever virus	3 + HEPA	3 + HEPA	3 + HEPA	vaccine
Bacteria				
Bacillus anthracis	2	2-3	2-3	vaccine
Brucella abortus, B. melitensis, B. suis	2	3	3	
Burkholderia (Pseudomonas) mallei	2	2-3	3	
Burkholderia (Pseudomonas) pseudomallei	2	2-3	3	
Clostridium botulinum	2	2-3	2-3	toxoid (IND)
Francisella tularensis	2	3	3	vaccine (IND)
Yersinia pestis	2	2-3	2-3	vaccine
Rickettsiae				
Coxiella burnetii	2	3	3	vaccine (IND)
Rickettsia prowazekii	2	3	2-3	
Rickettsia rickettsii	2	3	2-3	
Fungi				
Coccidioides immitis	2	3	2-3	

CONTENTS OF APPLICATION FOR REGISTRATION
Laboratory Registration and Select Agent Transfer Tracking System

Instructions and forms may be downloaded separately (PDF format) from:
http://www.cdc.gov/od/ohs/lrsat%20tracking%20II.htm

TRANSFERRING SELECT AGENTS - USING FORM EA-101

Procedure for transfer of a select agent

The purpose of the CDC EA-101 form is to provide a method for the documentation of the transfer of a select agent. An EA-101 form must be completed for each transfer of a select agent. A copy of each EA-101 must be kept by the responsible facility official (RFO) for five years.

Prior to transferring a select agent

Before a select agent is transferred, both sender (transferor) and receiver (requestor) facilities must be registered with the CDC. The requestor fills out blocks 1 and 2 of the EA-101 form and submits it, with a copy of the requesting facility's registration certificate, to the transferor. The transferor's responsible facility official (RFO) must verify with the requestor's RFO, and if appropriate, with the CDC, that the requesting facility: (1) retains a valid, current registration for the select agent being requested; (2) the person requesting the select agent is an employee of the requesting facility; and, (3) that the proposed use of the agent by the requestor is correctly indicated on CDC Form EA-101. For biosecurity reasons, CDC recognizes that the select agent registration certificate does not have information regarding which specific select agent(s) a facility is registered for with the CDC. If the transferor cannot verify the registration status of the requestor, there is suspicion that the agent may not be used for the requested purpose, or there are any other concerns, then the transferor should consult with the CDC.

Transfer:

(a) Shipment of the select agent to the requestor

- After the transferor has verified the information in blocks 1 and 2 of the EA-101, then the transferor ships the material to the receiver. The transferor fills out Section 3 and the shipping information in Section 4, including the date the agent was shipped. Select agents must be packaged, labeled, and shipped in accordance with all federal (e.g., 42 CFR 72 and 49 CFR 100-180) and international (IATA) regulations. It is highly recommended that the transferor utilize a mechanism for tracking the movement of select agents shipped. Return receipt is required by law for some select agents listed in 42 CFR part 72.3(f).[1]

(b) Receipt of the select agent by the requestor

- The RFO from the receiver's facility must acknowledge receipt of the agent to the transferor by telephone or otherwise electronically within 36 hours of receipt. The receiver's RFO is also required to provide a paper copy or facsimile transmission of receipt to the transferor within three business days of receipt of the agent.

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[1] *Coccidioides immitis*; Ebola virus; *Francisella tularensis*; Viruses causing HPS; CCHF; Junin Virus; Machupo virus; Lassa virus; Marburg virus; *Burkholderia mallei*; *Burkholderia pseudomallei*; Tick-borne encephalitis virus complex; Variola major virus; *Yersina pestis*

(c) Transmittal of the EA-101 form to the CDC

- After telephonic acknowledgment of receipt of the agent, the transferor writes in the date the agent was received in Section 4 of the EA-101 form. The transferor is required to provide a completed paper copy or facsimile transmission of the EA-101 form within 24 hours to the CDC. In addition, we recommend that a completed copy of the CDC Form EA-101 be sent to the receiver as well at the same time. This not only provides the receiver with a courtesy copy of the completed form, but assists the receiver if and when they need to complete Section 5 in the future (below).

Destruction or depletion of a select agent

When a select agent from a transfer is depleted or destroyed, the RFO of the facility must complete Section 5 of the CDC Form. A copy or FAX of the EA-101 form must be sent to the CDC.

Table 1. Steps in transferring a select agent

Requestor RFO	**Transferor RFO**
1. Completes agent description (Block 1)	
2. Completes requestor information (Block 2)	
3. Faxes form EA-101 and registration certificate to transferor	
	4. Verifies registration information
	5. Completes transferor information
	6. Completes shipping information
	7. Oversees packaging and shipment of agent to requestor. Sends shipment.
8. Receives agent	
9. Requestor RFO notifies transferor RFO of receipt of agent via facsimile or telephone within 36 hours (or provides paper copy to the transferor RFO within 3 days)	

Requestor RFO	**Transferor RFO**
	10. Transferor enters date agent received in block 4
	11. Transferor faxes completed form EA-101 to CDC within 24 hours
12. Retains paper record for 5 yr, or retains record 5 yr after agent consumed or destroyed, whichever is longer	12. Retains paper record for 5 yr, or retains record 5 yr after agent consumed or destroyed, whichever is longer

TRANSFER PROCESS FOR EXEMPTED CLIA-CERTIFIED LABORATORIES

The rule (42 CFR 72.6) specifically exempts clinical laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) that utilize select agents for diagnostic, reference, verification, or proficiency testing purposes. In addition, the rule provides procedures for facilities that are not CLIA laboratories but are transferring or receiving select agents to or from a CLIA laboratory. No additional paperwork on behalf of CLIA laboratories is required by this final rule. CDC will accept a CLIA certification number on CDC Form EA-101 in lieu of the required institutional registration number, as stipulated in this final rule.

This exemption is found in 42 CFR 72.6 (h) (2) and the transfer procedure for sending a select agent from a registered facility to a CLIA laboratory are found in 42 CFR 72.6 (h) (3); both are repeated here for your convenience:

(2) Exemption of CLIA certified laboratories: Clinical laboratories certified under the Clinical Laboratory Improvement Amendments of 1988, (42 U.S.C. 263a) (CLIA), that utilize these select agents for diagnostic, reference, verification, or proficiency testing purposes are exempt from the provisions of Sec. 72.6.

(3) Procedures for facilities that are not CLIA laboratories but are transferring or receiving select agents to or from a CLIA laboratory: Facilities that are not CLIA laboratories but are transferring or receiving select agents to or from a CLIA laboratory must comply with the following provisions. (No additional paperwork on behalf of CLIA laboratories is required by this section.)

- *(i) Prior to transferring a select agent subject to this part to a CLIA laboratory for diagnostic, reference, verification, or proficiency testing purposes, the transferor must:*
  - *(A) Provide the following information on CDC Form EA-101:*
    - *(1) The name of the requestor and requesting facility;*
    - *(2) The name of the transferor and transferring facility;*
    - *(3) The name of the transferor's responsible facility official;*
    - *(4) The requesting facility's CLIA certification number (which the transferor must verify as valid and current with the registering entity);*
    - *(5) The transferring facility's registration number;*
    - *(6) The name of the agent(s) being shipped;*
    - *(7) The proposed use of the agent(s); and*
    - *(8) The quantity (number of containers and amount per container) of the agent(s) being shipped.*

(B) Verify receipt of the agent with the CLIA laboratory and note such receipt on CDC Form EA-101;

(C) Transmit a copy of the form, signed by the transferror and the responsible facility official representing the transfering facility, to the registering entity holding the transferring facility's registration; and

(D) Retain a copy of CDC Form EA-101 in accordance with Sec. 72.6(d)(3) and Sec. 72.6(d)(4).

(ii) Prior to receiving a select agent listed in Appendix A of this part from a CLIA laboratory, the requestor must be registered in accordance with Sec. 72.6(a) and comply with the following requirements:

(A) Provide the following information on the CDC Form EA-101:

(1) The name of the requestor and requesting facility;

(2) The name of the transferor and transferring facility;

(3) The name of the requestor's responsible facility official;

(4) The transferring facility's CLIA certification number;

(5) The requesting facility's registration number;

(6) The name of the agent(s) being shipped;

(7) The proposed use of the agent(s); and

(8) The quantity (number of containers and amount per container) of the agent(s) being shipped.

(B) Upon receiving the agent, note such receipt on CDC Form EA-101;

(C) Transmit a copy of CDC Form EA-101, signed by the requestor and the responsible facility official representing the requesting facility, to the registering entity holding the requesting facility's registration;

(D) Retain a copy of the CDC Form EA-101 in accordance with Secs. 72.6(d)(3) and 72.6(d)(4);

(E) Comply with the disposal requirements of Sec. 72.6(i) and all other sections of this part when subsequently transferring the agent.

Since CLIA-certified laboratories that are using select agents for exempt purposes are not required to register with CDC, our office cannot verify that a CLIA laboratory is authorized to receive, or is capable of handling, a select agent. When a registered facility receives a request from a CLIA-certified laboratory for a select agent, we recommend that the CLIA laboratory provide you with a copy of their current CLIA certificate, and a signed statement that their facility is capable of safely handling this select agent, and that it will only be used for the purposes that are exempt from this regulation.

FOR MORE INFORMATION

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